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Incyte Genomics
3160 Porter Drive
Palo Alto, CA 94304

EXAMINER
HELMS, LARRY RONALD

ART UNIT	PAPER NUMBER
1642	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/807,452	Applicant(s) TANG ET AL.	
	Examiner Larry R. Helms	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-44* is/are pending in the application.

4a) Of the above claim(s) *21,22 and 31-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's election with traverse of Group 28, newly added claims 23-30, in Paper No. 11 is acknowledged. The traversal is on the ground(s) that unity of invention must be applied in the national stage and polypeptides and polynucleotides have a unity of invention and cite example 17 of Annex B of administrative instructions (see pages 7-8 of response). This is not persuasive. Example 17 is a specific example and applicants claims do not corresponds to the example. The clams in the instant application are not just to a single DNA or polypeptide but to biological fragments and immunogenic fragments. The response states that unity of invention exists among SEQ ID NO:12 and 31. In response to this argument, the polynucleotide is structurally distinct from the polypeptide as stated in the restriction requirement. The response states that there would be minimal burden to search claims drawn to methods of using the polynucleotides (see pages 11-12 of response). In response to this argument the methods are distinct and require different method steps, and different considerations and different searches (methods of detection in class 435/6 vs. method of treatment in 514/44, for example). As to the question of burden of search, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not co-extensive and is much more important in evaluating the burden of search. Clearly different searches and issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper and is made **FINAL**.

2. Claims 21-22, 31-44 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions. Applicant timely traversed the restriction (election) requirement in Paper No. 11.

3. Claims 23-30 are under examination.

Specification

4. The disclosure is objected to because of the following informalities:

a. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code on page 18, lines 13 and 17, for example. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

b. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed, such as polynucleotides encoding proliferation and apoptosis related proteins.

c. The first line of the specification should indicate the proper relationship of all applications, such as CON, CIP, or DIV.

Appropriate correction is required.

Claim Objections

5. Claims 23-29 are objected to because of the following informalities: The claims are dependent on non-elected claims. Although the claims depend from non-elected claims, the claims will be examined with all the limitations of claims 21-22.

Appropriate correction is required.

Claim Rejections - 35 USC § 101

6. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

7. Claims 23-30 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a substantial asserted utility or a well established utility.

Claims 23-30 are directed to isolated and purified polynucleotides encoding proliferation and apoptosis related proteins (PROAP), vectors comprising same, host cells comprising the vectors, and methods of recombinant producing the encoded polypeptides. The specification discloses the isolation of SEQ ID NO:31 that encodes SEQ ID NO:12 (see tables 2 and 3). SEQ ID NO:31 which encodes SEQ ID NO:12 is disclosed to be related to TRE oncogene product (see Table 2). Based on the structural similarity, the specification asserts that the newly disclosed polynucleotide would have the utility of having similar activities.

The assertion that the disclosed PROAP have biological activities similar to known oncogenes is not credible in the absence of supporting evidence, because the relevant literature reports numerous examples of polypeptide or polynucleotide families

wherein individual members have distinct, and even opposite, biological activities. For example, Tischer et al. (U.S. Patent 5,194,596) establishes that VEGF (a member of the PDGF, or platelet-derived growth factor, family) is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occurring PDGF which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (column 2, line 46 to column 3, line 2). The differences between PDGF and VEGF are also seen *in vivo*, wherein endothelial-pericyte associations in the eye are disrupted by intraocular administration of PDGF but accelerated by intraocular administration of VEGF (Benjamin et al., 1998, Development 125:1591-1598; see Abstract and pp. 1594-1596). Vukicevic et al. (1996, PNAS USA 93:9021-9026) disclose that OP-1, a member of the TGF-β family of proteins, has the ability to induce metanephrogenesis, whereas closely related TGF-β family members BMP-2 and TGF-β1 had no effect on metanephrogenesis under identical conditions (p. 9023, paragraph bridging columns 1-2). See also Massague, who reviews other members of the TGF-β family (1987, Cell 49:437-8, esp. p. 438, column 1, second full paragraph to the end). Similarly, PTH and PTHrP are two structurally closely related proteins which can have opposite effects on bone resorption (Pilbeam et al., 1993, Bone 14:717-720; see p. 717, second paragraph of Introduction). Finally, Kopchick et al. (U.S. Patent 5,350,836) disclose several antagonists of vertebrate growth hormone that differ from naturally occurring growth hormone by a single amino acid (column 2, lines 37-48).

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small

domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts. Finally, Bowie et al. (1990, Science 247:1306-1310) state that determination of three dimensional structure from primary amino acid sequence, and the subsequent inference of detailed aspects of function from structure is extremely complex and unlikely to be solved in the near future (p. 1306). Thus, the specification fails to support the asserted substantial utility of oncogene activity.

The specification does not support a substantial utility regarding the claimed polynucleotides encoding oncogene and variants thereof for purposes unrelated to the asserted biological activity. For example, the specification asserts that the claimed polynucleotides are involved in cell proliferative and immunological and reproductive disorders (see page 22) based solely on the structural similarity. The specification does not disclose a correlation between any specific disorder and an altered level or form of the claimed polynucleotides and only discloses that SEQ ID NO:31 is expressed in gastrointestinal, nervous, and reproductive tissue and cancerous, inflammation and cell proliferative tissue but does not indicate any correlation (see Table 3). Also, the specification does not predict whether the claimed polynucleotides would be overexpressed or underexpressed in a specific, diseased tissue compared to the healthy tissue control. The specification contains assertions that the claimed polynucleotides can be used in gene expression monitoring assays, which are used in the art for drug development and toxicology studies. However, without a disclosure of a particular disease state in which the claimed polynucleotides are expressed at an

altered level or form, it would be impossible to determine what the results of a gene expression monitoring assay mean. For example, if a compound is tested on a microarray comprising the claimed polynucleotides and affects expression of the polynucleotides negatively, it cannot be determined if that means that the compound is a potential good drug for a disease or would acerbate the disease if administered. The test results also would not have meaning in terms of what specific disease is relevant. The asserted utility in gene expression monitoring assays is thus not substantial, because significant further research would have to be conducted to determine which diseases correlate with altered forms or levels of the claimed polynucleotides, and whether the claimed polynucleotides are overexpressed or underexpressed in the diseased tissue. Furthermore, since any expressed polynucleotide can be added to a microarray for gene expression monitoring, the asserted utility is not specific to the claimed polynucleotides.

The instant application has failed to provide guidance as to how one of skill in the art could use the claimed invention in a way that constitutes a credible, specific and substantial utility. The proposed uses of the claimed invention are simply starting points for further research and investigation into potential practical uses of the claimed nucleic acids. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696.

8. Claims 23-30 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 101

9. Claim 27 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The claim as written, does not sufficiently distinguish over a cell that is transformed or a cell that has been placed in an organism such as gene therapy because claim does not particularly point out any non-naturally occurring differences between the claimed cell and compositions of cells that exist in a host.

In the absence of the hand of man, the cell is considered non-statutory subject matter (Diamond v. Chakrabarty, 206 U.S.P.Q. 193 (1980)). It should be noted that the mere purity of a naturally occurring product does not necessarily impart patentability (Ex parte Siddiqui, 156 U.S.P.Q. 426 (1966)). However, when purification results in a new utility, patentability is considered (Merck Co. v. Chase Chemical Co., 273 F.Supp 68 (1967), 155 USPQ 139, (District Court, New Jersey, 1967)). Amendment of the claims to recite "an isolated or purified" cell or similar language would obviate this rejection.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 23, 26-28, 30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 23 (which depends on claim 21) and 30 has been amended to recite "a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:12". The specification only teaches SEQ ID NO:12. The general knowledge in the art concerning naturally occurring sequences does not provide any indication of how the structure of one sequence is representative of unknown sequences. Reiger et al. (Glossary of Genetics and Cytogenetics, Classical and Molecular, 4th Ed., Springer-Verlay, Berlin, 1976) clearly define alleles as one of two or more alternative forms of a gene occupying the same locus on a particular chromosome... and differing from other alleles of that locus at one or more mutational sites (page 17). Thus, the structure of naturally occurring sequences are not defined. With the exception of SEQ ID NO:1 the skilled artisan cannot envision the detailed structure of the encompassed polypeptides and therefore conception is not achieved

until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Thus, one of skill in the art would not understand that the applicant had possession of the claimed invention at the time the instant application was filed.

12. Claims 23, 26-28, 30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to an isolated polynucleotide that encodes a polypeptide that is at least 90% identical to SEQ ID NO:12 or a polynucleotide that is 90% identical to SEQ ID NO:31 or a polynucleotide that encodes a biologically active fragment of SEQ ID NO:12 or an antigenic fragment of SEQ ID NO:12.

The specification teaches only SEQ ID NO:31 which encodes SEQ ID NO:12. The specification contemplates a function of SEQ ID NO:12 and 31 based on sequence

comparison. Besides the sequence comparison, there is no sufficient evidence showing the relationship of SEQ ID NO:12 or 31 to TRE oncogene product. A mere factor of similarity of the sequences does not predict the activity of the new protein and even a small difference between sequences could render substantial differences between the activities of the proteins.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, the replacement of a single lysine at position 118 of the acidic fibroblast growth factor by a glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al, Journal of Cell Biology Vol 111 November 1990 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with asparagine, did not affect biological activity while the replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (see Lazar et al Molecular and Cellular Biology Mar 1988 Vol 8 No 3 1247-1252). Replacement of the histidine at position 10 of the B-chain of human insulin with aspartic acid converts the molecule into a superagonist with 5 times the activity of nature human insulin. Schwartz et al, Proc Natl Acad Sci USA Vol 84:6408-6411 (1987). Removal of the amino terminal histidine of glucagon substantially decreases the ability of the molecule to bind to its receptor and activate adenylate cyclase. Lin et al Biochemistry USA Vol 14:1559-1563 (1975).

These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of the protein.

The claims encompass a biologically active fragment or an immunogeneic fragment of SEQ ID NO:12. Given the undue experimentation required to use the claimed polynucleotide or polypeptide, it would also require undue experimentation to make and/or use immunogenic portions or biologically active portions of the polypeptides. Additionally, given the lack of description of the regions of the polypeptides which are definitive of specific antigenic regions or which are required to maintained identifying characteristics, it would require undue experimentation to obtain immunogenic portions, even if the polypeptides were enabled. Additionally, because there is no evidence identifying the biologically activity domain, it would also require undue experimentation to obtain biologically active fragments of SEQ ID NO:12. There is no guidance regarding which portions of the polypeptide are immunogenic, definitive or active. The tertiary structure of SEQ ID NO:12 has not been determined and as such all polypeptides could be immunogenic but not all polypeptides would be expected to produce antibodies that would be used because if the antibodies are directed against a buried sequence in SEQ ID NO:12, these antibodies could not be used. The method disclosed in the specification for the determination of the biological activity was not actually used in any method to determine the biological activity of SEQ ID NO:12, and as such one skilled in the art would not know how to determine a "biologically active" polypeptide.

Therefore, in view of the unpredictability in the art of protein chemistry as indicated above, and in view of the lack or guidance in the specification and in view of

the broadly claimed invention, it would require undue experimentation to practice the broadly claimed invention.

Conclusion

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

15. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879

LARRY R. HELMS, PH.D
PRIMARY EXAMINER